# PART 2: NON-TECHNICAL ABSTRACT

The purpose of this clinical research study is to examine the safety and potential ability of a new study treatment to stimulate the growth of new blood vessels from existing blood vessels (a process called angiogenesis) to improve the flow of blood within the legs of patients with critical limb ischemia (CLI), a severe form of peripheral vascular disease (PVD). This treatment, named *Ad2/HIF-1-alpha/VP16*, is a new kind of gene transfer therapy which was developed by the sponsor of this study, Genzyme Corporation. This study treatment transfers a gene into cells within the patient's leg, which cause the cells to produce a substance called Hypoxia Inducible Factor-one-alpha (HIF-1-alpha).

The gene for HIF-1-alpha will be introduced into the cells by using a modified virus called an adenovirus. Adenovirus (Ad2) is a common virus found in human airways and, in its normal state, can reproduce and cause a cold. This virus (Ad2/HIF-1-alpha/VP16) has been altered so that it can not reproduce. The production of HIF-1-alpha is part of the patient's response to low amounts of oxygen caused by reduced blood flow. When HIF-1-alpha enters these cells it causes the cells to produce and release growth factors like vascular endothelial growth factor (VEGF) and other substances. These growth factors (called angiogenic growth factors) have the ability to stimulate the growth of new blood vessels from existing blood vessels and, as a result, increase the flow of blood carrying oxygen to these cells.

These clinical research studies will look at whether different doses of Ad2/HIF-1-alpha/VP16 can be tolerated safely. In addition, the study will measure how well the Ad2/HIF-1-alpha/VP16 works by measuring levels of the angiogenic growth factor, VEGF, in the blood, and by using magnetic resonance angiography (MRA) and other techniques to measure any new angiogenic blood vessel growth after treatment with Ad2/HIF-1-alpha/VP16. Finally, this research study will look at the response of the disease to treatment with Ad2/HIF-1-alpha/VP16 by taking blood flow measurements within the leg, changes in non-healing ulcers, and the assessments of leg pain.

The first study (PVD-HIF-001-99) will be a 60 day Phase I Escalating Dose study that will examine the preliminary safety and bioactivity of three doses of Ad2/HIF-1-

alpha/VP16. The results from the three treatment groups will be compared to a placebo group. A placebo group is included in this study because, although unlikely, it is theoretically possible that angiogenesis could be stimulated by inflammation and subsequent wound healing from an intramuscular injection of a fixed volume of fluid.

Upon completion of PVD-HIF-001-99, patients will be enrolled in an Extension Study (PVD-HIF-002-99) and followed periodically for one year post-treatment to evaluate the longer-term safety, bioactivity, and preliminary efficacy of Ad2/HIF-1-alpha/VP16. Patients will not receive any investigational product in this extension study. It is important to the future development of Ad2/HIF-1-alpha/VP16 that any favorable effects are maintained for a sufficient period of time to benefit the patient.

Given the poor prognosis for patients with intractable chronic limb ischemia, patients randomized to placebo in the Phase I Escalating Dose study (PVD-HIF-001-99) will be given the option to be rolled over into an active treatment protocol following the completion of that study. These patients will be treated with the highest safe dose from that study. This Roll-Over treatment study (PVD-HIF-003-99) for patients previously randomized to placebo will also be a 60 day study followed by automatic enrollment into the extension study (PVD-HIF-002-99) for one year follow up.